



Telomere Length and Oxidative Stress in Patients with ST-Segment Elevation and Non-ST-Segment Elevation Myocardial Infarction

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Abstract

Purpose The telomere length is shown to act as a biomarker, especially for biological aging and cardiovascular diseases, and it is also suggested that with this correlation, increased exposure to the oxidative stress accelerates the vascular aging process. Therefore, this study aims to understand the correlation between the plasma oxidative stress index (OSI) status and leukocyte telomere length (LTL) and cardiologic parameters between the ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation myocardial infarction (NSTEMI) groups.

Method One hundred one newly diagnosed patients with STEMI ($n = 55$) and NSTEMI ($n = 46$) were included in the study, along with 100 healthy controls who matched the patients in terms of age and gender. Plasma total anti-oxidant status (TAS), total oxidant status (TOS), and LTL were measured.

Results When LTL, TAS, TOS, and OSI values were evaluated between the patient and control group, OSI ($p = 0.000$) and LTL ($p = 0.05$) values were statistically significant in the patient group compared to the control group. Evaluation was conducted to understand whether there is a difference between the STEMI and NSTEMI groups. The plasma OSI ($p = 0.007$) and LTL ($p = 0.05$) were found to be significantly lower in STEMI patients. However, LTL and OSI results were not statistically significant in NSTEMI patients.

Conclusion This is the first study evaluating telomere length and oxidative stress in STEMI and NSTEMI patients in Turkey. Our results support the existence of short telomere length in STEMI patients. Future studies on telomere length and oxidative stress will support the importance of our findings.

Keywords

Acute myocardial infarction · Non-ST-segment elevation myocardial infarction · Oxidative stress · ST-segment elevation myocardial infarction · Telomere length

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1 Introduction

Acute myocardial infarction (AMI) is one of the leading causes of death in the world. The majority of deaths are associated with acute coronary syndromes (ACS) and their complications. In particular, circulatory system diseases account for 31.9% of total death cases (Turkish Statistical Institute 2018). Patients with myocardial infarction due to ACS are classified according to their electrocardiographic data as ST-segment elevation myocardial infarction or non-ST-segment elevation myocardial infarction. STEMI is a clinical condition that develops as a result of total occlusion of the coronary artery. If early revascularization cannot be achieved after the total occlusion of the thrombus and the ischemia resulting from it, a myocardial necrosis occurs, which spreads from the endocardium to the epicardial area, starting from the 20th min. NSTEMI is a condition in which myocardial ischemia occurs, but myocardial damage and necrosis are limited due to temporary or partial occlusion (Hamm et al. 2011).

Various factors such as age, gender, hypercholesterolemia, hypertension, diabetes mellitus (DM), family history, and smoking are known to increase the risk of ACS. Furthermore, studies have demonstrated that oxidative stress and telomere length are associated with increased cardiovascular risk and mortality (Yeh and Wang 2016; Siti et al. 2015). Telomeres are noncoding tandem repeat DNA sequences (TTAGGG), and their associated proteins are found at the ends of chromosomes. They protect chromosomes against degradation and against the loss of genetic material during cell division (Riethman 2008). Shorter telomere length is linked to age-related diseases such as cardiovascular disease (CVD), DM, hypertension, and cancer. Thus, it has been suggested that telomere length contributes to mortality in many age-related diseases and is a predictor of mortality (Yeh and Wang 2016; Haycock et al. 2014). Oxidative stress causes telomere loss in each cell division, and oxidative damage is less likely to be repaired in telomere DNA than in any part of the chromosome (Von Zglinicki 2002). Some systemic markers of

oxidative stress predict the clinical outcome in coronary artery disease. Systemic oxidative stress and inflammation associated with cardiovascular risk can accelerate telomere shortening. Experimental studies suggest that oxidative stress shortens TL in vitro and some studies support the use of TL as an independent marker of MI, but it is not clear whether the blood TL is tissue-specific or whether it is a global biomarker of oxidative stress in acute myocardial infarction (Siti et al. 2015; Von Zglinicki 2002; Margaritis et al. 2017). Although various studies have been carried on telomere length in CVD, only a few studies evaluated the relationship between the effect of leukocyte telomere length (LTL), plasma total antioxidant status (TAS), and total oxidant status (TOS) on clinical data in STEMI and NSTEMI patient groups (Haycock et al. 2014; Margaritis et al. 2017). In this study, we aimed to evaluate the results of telomere length along with the oxidative stress index (OSI) and clinical findings in STEMI and NSTEMI patient groups compared to healthy controls by testing the clinical predictive value of short telomere length in AMI risk groups.

2 Method

2.1 Ethical and Legal Aspects of the Research

The study was performed according to the principles of the Declaration of Helsinki. The ethical trial of this study was approved by the local ethics committee (document no: 2017-06/07). Informed consent was obtained from the patients and controls taking part in our research.

2.2 Study Population

In this case-control study, 101 patients were included, who were diagnosed with STEMI (n = 55) and NSTEMI (n = 46) at ages ranging from 43 to 67 years old. The control group was composed of 100 healthy volunteers who were age- and sex-matched to chosen patients. Special

attention was given to choose controls that did not have any previous CVD history. The STEMI and NSTEMI were diagnosed according to clinical guidelines previously reported (Thygesen et al. 2018). STEMI was defined in the new presence of ST elevation at the J-point with at least two contiguous leads (2.5 mm or more in men younger than 40 years of age, of 2 mm or more in men aged 40 years or older, or of 1.5 mm or more in women in leads V2 to V3 and/or of 1 mm) or in the new left bundle branch block seen in an electrocardiogram (ECG). NSTEMI was diagnosed by a rise or fall of troponin I and absence of persistent ST elevation seen via an ECG. All patients received standard care and underwent primary percutaneous coronary intervention within 2 h after being admitted to the hospital. Thus, use of dual therapy aspirin and a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) were available for all patients. We conducted clear exclusion criteria for patients by considering the following cases: active infection or chronic inflammatory disease, received fibrinolytic therapy, previous myocardial infarction, malignancy, major surgery required due to coronary artery bypass, chronic obstructive pulmonary disease, renal dysfunction, or hepatic disease. We performed transthoracic echocardiographic examination using an echocardiography device (Philips Affiniti 50, Philips Healthcare, the Netherlands) according to the recommendations of the American Society of Echocardiography (Baumgartner et al. 2017). We determined the left ventricular ejection fraction (LVEF) using the modified Simpson method (Horwitz 2001). BMI was calculated by dividing the body weight by the square of the neck (kg/m^2). All blood values of the participants were examined using the blood taken at the initial diagnosis period.

2.3 Coronary Angiography

Coronary angiography was performed through the right femoral arterial route using the standard Judkins method (Judkins 1968). We visualized

coronary arteries using cranial and caudal angles in the right and left oblique plane. Iopromide (Ultravist 370, Schering AG, Berlin, Germany) was used as the contrast agent for coronary angiography. Stenosis and lesion length in the coronary arteries were evaluated using the Digital Imaging and Communications in Medicine (DICOM) program. The SYNTAX scores were used to estimate extent and complexity of coronary lesions and were provided for all patients. The web-based program (www.syntaxscore.com) was used to calculate the SYNTAX score. The severity of coronary lesions was calculated using the Gensini score as a second method (Gensini 1983).

2.4 Measurement of TAS and TOS

The blood samples were collected from the femoral artery at initial diagnosis period before the coronary angiography. Plasma samples were collected during the study and stored at $-80\text{ }^{\circ}\text{C}$. Plasma TAS and TOS levels were measured by Erel's modification methods using commercially available kits (Rel Assay, Turkey). In serum samples, the normal value range for TAS was 1.20–1.50 mmol/L, and the normal value range for TOS was 4.00–6.00 $\mu\text{mol}/\text{L}$. The ratio of TOS to TAS was accepted as the oxidative stress index (OSI). For calculation, the resulting unit of TAS was converted to $\mu\text{mol}/\text{L}$, and the OSI value was calculated according to the following formula, $\text{OSI (arbitrary unit-AU)} = \text{TOS } (\mu\text{mol H}_2\text{O}_2 \text{ equivalent/L})/\text{TAS } (\mu\text{mol Trolox equivalent/L})$ (Erel 2004, 2005).

2.5 Measurement of Telomere Length

The blood samples were collected from the femoral artery at the time of initial diagnosis before coronary angiography for an accurate evaluation of biological variables and stored at $-80\text{ }^{\circ}\text{C}$. Genomic DNA was isolated from peripheral

blood using the QIAamp DNA kit (QIAGEN, Germany). LTL was measured via the real-time quantitative polymerase chain reaction (RT-PCR) method based on the original study (Cawthon 2002). DNA concentrations of the samples were measured with a fluorometer (QFX, DeNovix, USA). DNA concentrations equaled 5 ng/μl in all samples. The relative telomere length was calculated as the ratio of telomere repeat signal (T) to single-copy gene, 36B4 (acidic ribosomal phosphoprotein P0, S), and copies (T/S ratio). The number of telomere repeats and the quantity of single-copy gene copies for each sample were defined in comparison to a reference sample in a telomere and a single-copy gene quantitative PCR, respectively. The resulting T/S ratio was proportional to the mean LTL. The detailed method is described in another study where T/S ratios were converted into base pairs (bp) with the following formula: $bp = 3,274 + 24,133([T/S - 0.0545]/1.16)$ (Verhoeven et al. 2014).

2.6 Statistical Analysis

The statistical analysis was performed using SPSS version 21.0 software (SPSS Inc., ILL Company, USA). Continuous variables were tested for normality using the Kolmogorov-Smirnov test. Continuous data were presented as mean ± standard deviation (SD) or mean (% 95 confidence interval). The Student's t-test was used to compare continuous variables with normal distributions. The Kruskal-Wallis test was used to compare variables with abnormal distributions, and the Pearson (for data with normal distribution) and Spearman correlation analyses (for data not showing normal distribution) were used for correlation analysis. Changes of LTL values, T/S ratio, and TAS, TOS, and OSI levels between groups were tested with one-way ANOVA and post hoc (Tukey) tests for multiple comparisons. Multiple linear regression analysis was conducted with the LTL and T/S ratio as a dependent variable baseline characteristics, and outcome parameters as independent variables. P-values of <0.05 were considered statistically significant.

3 Results

3.1 Characteristics of the Study Population and Telomere Length

A total number of 101 patients who were diagnosed with STEMI and NSTEMI and a total of 100 controls were enrolled in the study. The demographic, biochemical, and clinical data of the patient groups and control group were statistically compared (Table 1). Active smoking ($p = 0.006$), glucose ($p = 0.000$), urea ($p = 0.000$), creatinine ($p = 0.009$), triglyceride ($p = 0.001$), alanine aminotransferase (ALT) ($p = 0.003$), aspartate aminotransferase (AST) ($p = 0.009$), CRP ($p = 0.009$), white blood cell (WBC) ($p = 0.002$), left ventricular ejection fraction (LVEF) ($p = 0.001$), and aorta diameter ($p = 0.016$) values were statistically significant in the patient group compared to the control group. SYNTAX and Gensini scores were also evaluated within the patient groups. A SYNTAX score of 0–22 is considered to be low, 23–32 as medium, and 33 and above as high (Neumann et al. 2019). According to the SYNTAX score, both groups were in the low-risk group. The Gensini score of the patient groups was calculated as 48.2 in NSTEMI and 65.6 in STEMI. Gensini score was found to be higher in STEMI. When the two groups were compared, both SYNTAX ($p = 0.016$) and Gensini ($p = 0.004$) scores were found to be significantly higher in the STEMI group. When TAS, TOS, OSI, and LTL values were compared between the patient and control groups, LTL ($p = 0.05$) and OSI ($p = 0.000$) values were found to be significant in the patient group. When the correlation data was examined in the patient group, a strong and positive correlation was detected between LTL and T/S with TOS ($p = 0.008$, $r = 0.212$; $p = 0.008$, $r = 0.213$), OSI ($p = 0.045$, $r = 0.161$; $p = 0.047$, $r = 0.160$), and troponin I ($p = 0.039$, $r = 0.206$; $p = 0.039$, $r = 0.205$), respectively (Table 2). For the NSTEMI and STEMI groups, the results of the regression analysis regarding the comparison of the TAS, TOS, OSI, LTL, and T/S ratio values to demographic findings of the groups are presented in Table 3.

Table 1 Participants' demographic characteristics

	NSTEMI patients	STEMI patients	Control group	<i>p</i> value
Participants (n)	46	55	100	
<i>Risk factors</i>				
Age (years)	58.7 ± 8.9	57.3 ± 9.3	57.07 ± 9.5	0.185
Male gender (%)	58.7	69.1	46.3	0.054
BMI (kg/m ²)	24.6 ± 2.9	23.4 ± 2.9	23.1 ± 2.6	0.191
Diabetes mellitus (%)	37.0	41.8	33.3	0.656
Hypertension (%)	69.6	54.5	50	0.124
Hyperlipidemia (%)	41.3	49.1	33.3	0.248
Active smoking (%)	43.5	52.7	24.1	0.006 ^a
Family history (%)	50.0	56.4	33.3	0.022 ^a
Systolic blood pressure (mmHg)	131.3 ± 15.6	129.8 ± 18.5	127.6 ± 12.4	0.510
Diastolic blood pressure (mmHg)	79.2 ± 9.8	80.7 ± 15.5	79.0 ± 5.6	0.285
Heart rate (beats per minute)	80.2 ± 10.5	77.2 ± 6.6	78.7 ± 7.4	0.324
<i>Biological data on admission</i>				
Glucose (mg/dl)	143.2 ± 64.1	151.8 ± 66.3	110.1 ± 35.6	0.000 ^a
Urea (mg/dL)	23.6 ± 7.9	31.2 ± 41.1	16.7 ± 6.1	0.000 ^a
Creatinine (mg/dL)	1.3 ± 2.8	1.2 ± 1.5	0.80 ± 0.1	0.009 ^a
Total cholesterol (mg/dL)	201.2 ± 41.9	200.7 ± 90.1	199.8 ± 43.5	0.427
Triglycerides (mg/dL)	170.5 ± 93.9	125.6 ± 80.0	165.0 ± 72.2	0.001 ^a
HDL cholesterol (mg/dL)	47.1 ± 24.6	47.4 ± 22.8	47.7 ± 10.1	0.103
LDL cholesterol (mg/dL)	117.4 ± 38.7	138.7 ± 116.4	115.6 ± 33.2	0.387
ALT (U/l)	26.9 ± 26.8	27.5 ± 15.1	19.9 ± 10.5	0.003 ^a
AST (U/l)	38.5 ± 29.1	58.6 ± 55.8	18.7 ± 7.2	0.000 ^a
CRP (mg/L)	11.5 ± 24.4	9.9 ± 18.2	3.7 ± 3.6	0.000 ^a
WBC (10 ³ /mm ³)	9.0 ± 2.4	9.6 ± 2.7	7.9 ± 2.3	0.002 ^a
Lymphocytes (10 ³ /mm ³)	2.4 ± 0.8	2.5 ± 1.8	2.3 ± 0.9	0.632
Hemoglobin (g/dL)	14.0 ± 1.8	14.6 ± 4.8	14.3 ± 1.6	0.661
Hematocrit (%)	41.2 ± 7.8	48.2 ± 46.5	42.7 ± 4.6	0.837
Platelets (10 ³ /mm ³)	237.9 ± 63.2	250.6 ± 68.1	264.3 ± 58.2	0.131
Troponin I (ng/L)	1775.8 ± 2889.3	5865.7 ± 10730.9	–	
CK (U/L)	136.8 ± 149.5	293.4 ± 439.6	–	
CK-MB (U/L)	41.8 ± 54.3	85.5 ± 109.9	–	
<i>Transthoracic echocardiography values</i>				
LVEF (%)	53.1 ± 6.6	51.2 ± 8.3	56.2 ± 5.2	0.001 ^a
Aorta diameter (cm)	2.5 ± 0.5	2.6 ± 0.6	2.3 ± 0.4	0.016 ^a
Left atrium diameter (cm)	3.6 ± 0.3	3.6 ± 0.4	3.6 ± 0.3	0.966
LVEDD (cm)	4.6 ± 0.5	4.6 ± 0.7	4.4 ± 0.7	0.064
LVESD (cm)	2.8 ± 0.6	2.9 ± 0.7	3.1 ± 0.7	0.233
IVSd (cm)	1.1 ± 0.1	1.2 ± 0.2	1.1 ± 0.2	0.787
<i>Coronary angiography data</i>				
Number of affected vessels			–	
1 (%)	48.6	30.9		
2 (%)	37.1	40.0		
3 (%)	14.3	29.1		
Culprit vessel			–	
No (%)	4.8	0		
LAD (%)	35.7	47.3		
LCX (%)	31.0	16.4		
RCA (%)	28.6	36.4		

(continued)

Table 1 (continued)

	NSTEMI patients	STEMI patients	Control group	<i>p</i> value
Lesion length (mm)	19.8 ± 5.7	23.5 ± 7.0	–	
Reference vessel diameter (mm)	2.98 ± 0.4	2.92 ± 0.45	–	
Lesion location			–	
Proximal (%)	21.7	32.7		
Mid (%)	60.9	49.1		
Distal (%)	17.4	18.2		
Percentage of lesion vessel stenosis (%)	95.76 ± 4.33	99.21 ± 3.05	–	
Gensini score	48.2 ± 32.6	65.6 ± 29.6	–	
SYNTAX score	15.7 ± 6.9	19.6 ± 8.7	–	
<i>Analysis data</i>				
TAS (mmolTroloxEquiv./L)	1.47 ± 0.29	1.51 ± 0.20	1.45 ± 0.26	0.339
TOS (µmol H ₂ O ₂ equiv./L)	5.48 ± 5.17	5.27 ± 4.51	5.34 ± 10.6	0.097
OSI (AU)	0.18 ± 0.39	0.05 ± 0.03	0.39 ± 0.93	0.000 ^a
LTL (bp)	5013.30 ± 531.65	4817.72 ± 296.01	5049.92 ± 662.17	0.05 ^a
T/S ratio	0.41 ± 0.25	0.32 ± 0.14	0.43 ± 0.32	0.079

Values presented as mean ± standard deviation

ALT alanine aminotransferase, *AST* aspartate aminotransferase, *CK* creatinine kinase, *CK-MB* creatinine kinase MB, *CRP* C-reactive protein, *HCT* hematocrit, *HDL* high-density lipoprotein, *IVSd* interventricular septal thickness, *LAD* left anterior descending artery, *LCX* left circumflex artery, *LDL* low-density lipoprotein, *LTL* leukocyte telomere length, *LVDD* left ventricular end-diastolic volume, *LVEF* left ventricular ejection fraction, *LVSD* left ventricular end-systolic volume, *OSI* oxidative stress index, *PLT* platelets, *RCA* right coronary artery, *TAS* total antioxidant status, *TOS* total oxidant status, *WBC* white blood cell

^aDemographic, clinical, and laboratory data of the study groups

As seen in Table 3, in the NSTEMI group, there was a statistically significant relationship between both LTL and T/S ratio in heart rate ($p = 0.018$), urea ($p = 0.003$), aortic diameter ($p = 0.05$), Gensini score ($p = 0.043$), TOS ($p = 0.018$), and OSI values ($p = 0.000$). On the other hand, results of the regression analysis of TAS, TOS, and OSI levels clearly stated that there was a statistically significant relationship between certain demographic data. TAS with triglyceride and CRP, TOS with hypertension and glucose, and OSI with gender, heart rate, and hemoglobin were found to be statistically significant (Table 3). After a detailed analysis of regression results relevant to LTL, T/S ratio, and demographic data of the STEMI group, it was found that the correlation between glucose ($p = 0.05$) and TOS ($p = 0.017$) values was statistically significant. In addition, TAS, TOS, OSI, and demographic data were evaluated based on regression analysis, and it was observed that the relationship between TAS with triglyceride ($p = 0.002$) and urea ($p = 0.009$) and OSI with urea ($p = 0.037$) were also statistically significant.

3.2 Oxidative Stress and Telomere Length

The STEMI and NSTEMI patients and control groups were compared in terms of TAS, TOS, and OSI values. In ANOVA analysis, a significant difference was found among groups at $p = 0.09$ confidence level. Multiple comparison tables were utilized to see which groups were statistically different from the others (Tukey Test). A comparison of the groups regarding the OSI value acknowledges that the figure for the STEMI group was statistically significant ($p = 0.007$) and is given in Table 4. The STEMI and NSTEMI patient groups and the control group were also assessed in terms of T/S ratio and LTL values, and a significant difference was found in the confidence level of $p = 0.047$ as a result of ANOVA analysis. Multiple comparison tables defined the level of differences across groups. Regarding analysis results (Tukey Test), it was noticed that there was a statistically significant difference between the control group and STEMI group ($p = 0.05$). When ANOVA

Table 2 Data showing significant correlation with TAS, TOS, OSI, LTL, and T/S ratio in patient group

		TAS	TOS	OSI	LTL	T/S ratio
Systolic blood pressure	r	0.192 ^a	0.003	-0.001	-0.014	-.015
	p	0.017	0.966	0.986	0.859	.853
Glucose	r	0.141	0.325 ^b	-0.106	0.082	0.85
	p	0.080	0.000	0.191	0.308	0.292
Urea	r	0.205 ^a	0.186 ^a	-0.079	0.148	0.149
	p	0.010	0.021	0.330	0.065	0.064
Creatinine	r	0.218 ^b	0.105	-0.023	0.013	0.013
	p	0.007	0.196	0.773	0.873	0.873
Triglycerides	r	0.277 ^b	0.051	0.130	0.107	0.108
	p	0.000	0.531	0.108	0.187	0.181
HDL cholesterol	r	-0.180 ^a	-0.144	0.048	-0.035	-0.033
	p	0.025	0.073	0.555	0.667	0.681
AST	r	0.192 ^a	0.096	-0.238 ^b	0.053	0.052
	p	0.017	0.237	0.003	0.512	0.519
CRP	r	0.196 ^a	0.207 ^b	-0.047	0.122	0.124
	p	0.015	0.010	0.557	0.131	0.125
Lymphocytes	r	-0.074	0.095	-0.170 ^a	-0.028	-0.029
	p	0.362	0.240	0.035	0.726	0.722
Troponin I	r	-0.004	0.110	-0.062	0.206 ^a	0.205 ^a
	p	0.971	0.275	0.539	0.039	0.039
CK	r	0.060	-0.083	-0.290 ^b	0.004	0.004
	p	0.558	0.413	0.004	0.969	0.971
CK-MB	r	0.158	-0.033	-0.298 ^b	0.063	0.065
	p	0.116	0.746	0.003	0.536	0.520
TOS	r	0.146	-	-0.116	0.212 ^b	0.213 ^b
	p	0.071	-	0.149	0.008	0.008
OSi	r	-0.150	-0.116	-	0.161 ^a	0.160 ^a
	p	0.062	0.149	-	0.045	0.047
LTL	r	0.098	0.212 ^b	0.161 ^a	-	1.000 ^b
	p	0.225	0.008	0.045	-	0.000
T/S ratio	r	0.098	0.213 ^b	0.160 ^a	1.000 ^b	-
	p	0.224	0.008	0.047	0.000	-

^aCorrelation is significant at the 0.05 level

^bCorrelation is significant at the 0.01 level

analysis was used to determine whether there were differences regarding LTL values between the groups, a significant difference was also especially observed in the $p = 0.047$ confidence level. Furthermore, the Tukey Test indicated a statistically significant difference between the control group and STEMI group ($p = 0.05$). As a result, in the STEMI group, approximately 232 base pairs of decreased telomere length were noted as a statistical difference, yet there seemed to be no meaningful difference considering the NSTEMI group. The regression analysis identified a statistically significant relationship between LTL and

T/S ratio with TOS in both NSTEMI and STEMI groups. OSI values showed significant regression with LTL and the T/S ratio only in the NSTEMI group (Table 3, Figs. 1 and 2).

4 Discussion

After measuring telomere length in 201 individuals from the patients with STEMI and NSTEMI and healthy controls, the study found that telomere length was shorter in STEMI patients than in the control group. As a

Table 3 P-values results of regression analysis in STEMI and NSTEMI groups

Risk factors	NSTEMI					STEMI				
	LTL	T/S ratio	TAS	TOS	OSI	LTL	T/S ratio	TAS	TOS	OSI
Male gender	>0.05	>0.05	>0.05	>0.05	0.008 ^a	>0.05	>0.05	>0.05	>0.05	>0.05
Hypertension	>0.05	>0.05	>0.05	0.022 ^a	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Diastolic blood pressure	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Heart rate	0.018 ^a	0.018 ^a	>0.05	>0.05	0.012 ^a	>0.05	>0.05	>0.05	>0.05	>0.05
Glucose	>0.05	>0.05	>0.05	0.014 ^a	>0.05	0.05 ^a	0.05 ^a	>0.05	>0.05	>0.05
Hemoglobin	>0.05	>0.05	>0.05	>0.05	0.038 ^a	>0.05	>0.05	>0.05	>0.05	>0.05
Triglycerides	>0.05	>0.05	0.01 ^a	>0.05	>0.05	>0.05	>0.05	0.002 ^a	>0.05	>0.05
Urea	0.003 ^a	0.003 ^a	>0.05	>0.05	>0.05	>0.05	>0.05	0.009 ^a	>0.05	0.037 ^a
CRP	>0.05	>0.05	0.003	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Aorta diameter	0.05 ^a	0.05 ^a	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
Gensini	0.043 ^a	0.043 ^a	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05	>0.05
LTL	–	0.000 ^a	>0.05	0.018 ^a	0.000 ^a	–	0.000 ^a	>0.05	0.017 ^a	>0.05
T/S ratio	0.000 ^a	–	>0.05	0.018 ^a	0.000 ^a	0.000 ^a	–	>0.05	0.017 ^a	>0.05
TAS	>0.05	>0.05	–	>0.05	>0.05	>0.05	>0.05	–	>0.05	>0.05
TOS	0.018 ^a	0.018 ^a	>0.05	–	>0.05	0.017 ^a	0.017 ^a	>0.05	–	0.000 ^a
OSI	0.000 ^a	0.000 ^a	>0.05	>0.05	–	>0.05	>0.05	>0.05	0.000 ^a	–

^aThe mean difference is significant at the 0.05 level

Table 4 Results of TAS, TOS, OSI, LTL, and T/S ratio values compared with control group

	Control	NSTEMI			STEMI	
	Mean difference ± std. deviation	Mean difference ± std. deviation		p value	Mean difference ± std. deviation	p value
TAS	1.45 ± 0.26	1.47 ± 0.29		0.92	1.51 ± 0.2	0.50
TOS	5.34 ± 10.6	5.48 ± 5.17		0.99	5.27 ± 4.51	0.99
OSI	0.39 ± 0.93	0.18 ± 0.39		0.17	0.05 ± 0.03	0.007 ^a
LTL	5049.92 ± 662.17	5013.30 ± 531.65		0.93	4817.72 ± 296.01	0.05 ^a
T/S ratio	0.43 ± 0.32	0.41 ± 0.25		0.93	0.32 ± 0.14	0.05 ^a

Values presented mean difference (standard deviation)

^aThe mean difference is significant at the 0.05 level

result of the length calculation, the difference was about 232 base pairs. However, no correlation was noticed between NSTEMI and LTL.

There are various studies conducted on the telomere including analysis of the codes of human biological lifetime. It was suggested that telomere length may be a predictor of age-related diseases such as ACS (Zee et al. 2009). Previous reports described that shorter LTL was associated with increased cardiovascular risk and mortality, and it was also predicted to increase proinflammatory activity and high-risk plaque morphology (Zee et al. 2009; Calvert et al.

2011). Studies showing the relationship between telomere shortness and coronary artery diseases in the literature were reported that aged endothelial cells were present in atherosclerosis lesions, and atherosclerotic coronary endothelial cells with coronary artery disease have shorter telomeres than patients without coronary artery disease, and thus, the term “short telomere-mediated aging” in atherosclerotic lesions was devised (Minamino et al. 2002; Ogami et al. 2004). This definition supported a causal link between telomere shortening and coronary artery diseases (Minamino et al. 2002). Shorter telomeres were

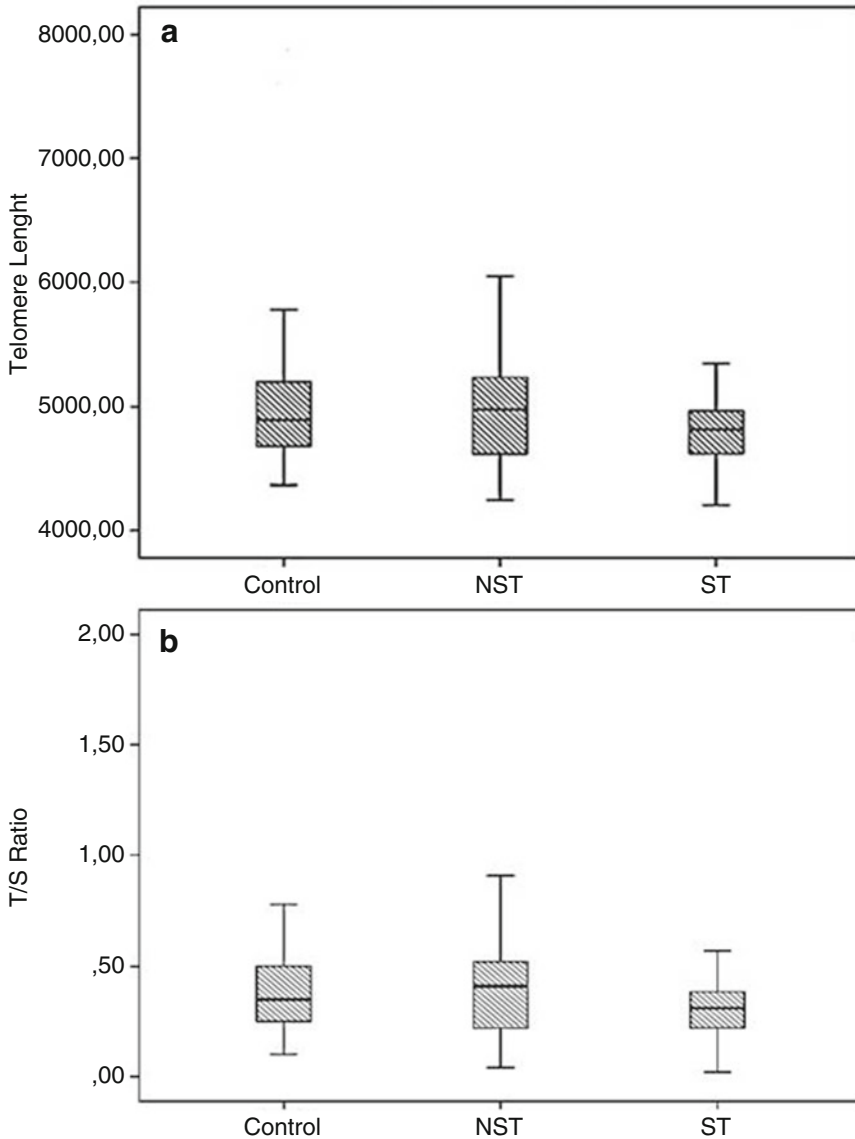


Fig. 1 Box plot of telomere length (a) and T/S ratio (b) in comparing groups of control, STEMI, and NSTEMI. The thick black line represents median values

being detected in patients with coronary artery diseases (Opstad et al. 2019), and there was an association between shorter telomeres and higher cardiovascular mortality (Cawthon et al. 2003). The study conducted by Cawthon et al., which measured telomere length in DNA samples of 143 people, found that those people with shorter telomeres had a threefold higher mortality rate from heart disease and an eightfold higher

mortality rate from infectious diseases (Cawthon et al. 2003). In a meta-analysis study, those with short telomeres had an increased risk of coronary artery disease when compared to those with a long telomere (Haycock et al. 2014). The association of short leukocyte telomere with increased stroke and myocardial infarction (D’Mello et al. 2015) was supported by the demonstration of increased cardiovascular risks in individuals

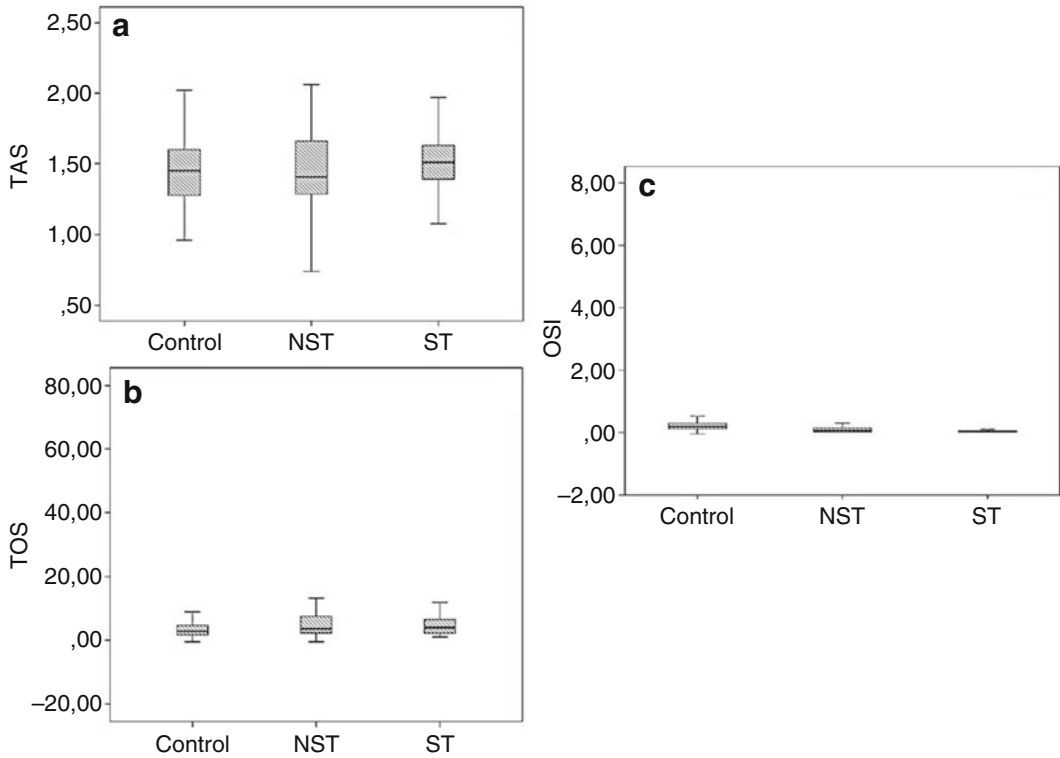


Fig. 2 Box plot of TAS (a), TOS (b), and OSI (c) levels in comparing groups of control, STEMI, and NSTEMI. The thick black line represents median values

with inherited short telomeres (Codd et al. 2013; Zhan et al. 2017). When telomere length was evaluated in both skeletal muscle and leukocyte, a relationship was found between LTL and atherosclerosis, but no relationship was found with muscle telomere length. The difference between leukocyte and muscle telomere length was due to the faster shortening of the leukocyte telomere in early life. It was observed that leukocyte telomere shortening in early life was a risk factor for coronary artery diseases and inherited short telomeres were not risk factors (Sabharwal et al. 2018).

A limited number of LTL studies have so far been reported in STEMI and/or NSTEMI patients. In a study with 353 participants, it was emphasized that LTL was not related after STEMI (Haver et al. 2015). In an incomplete but pre-published study including the NSTEMI group, shorter telomere length was evaluated to determine whether a biomarker predicts adverse incidents in elderly patients undergoing

percutaneous coronary intervention (Kunadian et al. 2016). Studies with larger numbers of STEMI and NSTEMI patients will further clarify the relationship between LTL and AMI.

Oxidative stress is caused by increased production of oxidizing products or a decrease in the effectiveness of antioxidant defenses. Various studies have confirmed that heart tolerance to oxidative stress decreases with age due to the reduction in the concentration of antioxidant enzymes. Furthermore, the development of oxidative stress contributes to vascular endothelial dysfunction with aging (Siti et al. 2015; Von Zglinicki 2002). It was shown that aging of endothelial cells of CVD patients with a heavy burden of risk factors starts even before telomeres are shortened to their threshold length (Voghel et al. 2007). Aging, hereditary genomic features, inflammation, and cumulative exposure of oxidative stress refer to the shortened presence of LTL (Siti et al. 2015; Von Zglinicki 2002; Margaritis

et al. 2017). Leukocyte telomere length is also associated with oxidative stress and inflammation (Bekaert et al. 2007). Increased oxidative stress and inflammation increase telomere shortening in somatic cells (Zhan et al. 2017; Daniali et al. 2013). Systemic oxidative stress and inflammation associated with cardiovascular risk can accelerate telomere shortening. Thus, the erosion rate hypothesis indicates that telomere shortening in adults is more important than hereditary telomere length (De Meyer et al. 2009). CVD, including STEMI and NSTEMI, are associated with increased oxidative stress as a result of impaired oxidant-antioxidant balance. As Gökdemir et al. showed, plasma TOS and OSI levels were significantly higher in NSTEMI patients, and it was thought to play a role along with the inflammatory process in the pathogenesis of NSTEMI (Gökdemir et al. 2013). Recent studies emphasize that oxidative stress may have an essential role in the pathogenesis of spontaneous reperfusion and development of atrial fibrillation in STEMI patients (Bas et al. 2017; Börekçi et al. 2016). Although there are no studies which show the direct relationship between oxidative stress and telomere length in STEMI and NSTEMI patients, there are certain studies emphasizing the effect of oxidative stress on short telomere length in CVD (Yeh and Wang 2016; Masi et al. 2016).

Since risk factors for CVD are associated with an increase in oxidative stress, in this study, we evaluated TAS, TOS, and OSI values in plasma of participants and found the OSI value to be lower in the STEMI group. OSI value was higher in the NSTEMI group compared to the STEMI group, but OSI was not found to be significant in NSTEMI group when compared with the control group. Studies have shown that oxidative stress indices increase after MI. NSTEMI alters biomarker levels, including oxidative stress indices (Kasap et al. 2007; Kundi et al. 2015). However, the low number of patients may have affected the results. Also interestingly, oxidative stress was found to be low in the NSTEMI group with a high SYNTAX score (≥ 23), and oxidative stress was found to be high in the NSTEMI group with

low SYNTAX score (< 23) (Kundi et al. 2015). We found the SYNTAX score was lower in the NSTEMI group compared to the STEMI group, and higher OSI scores were seen in the NSTEMI group than in the STEMI group.

According to the regression analysis, there was a significant correlation between LTL with OSI and TOS values in patients with STEMI. The reason why we found low OSI values in STEMI patients compared to control group was that one of the most critical factors determining the rupture sensitivity of atherosclerotic plaque is the inflammation that develops within the plaque. Depending on the severity of the injury in the atheroma plate, different ACS tables appear. Unless the injury in the atheroma plate is relatively large, the thrombus formed is predominantly thrombocyte, while fibrin content is low. This white thrombus usually does not completely occlude the coronary artery (NSTEMI). However, when thrombus caused by plaque rupture makes total occlusion of the coronary artery, ST elevations occur in the ECG, and all, or almost all, of the affected ventricular wall remains within the necrosis field. This condition is also referred to as transmural AMI (STEMI). The fibrin content of this red thrombus is high. Oxidative stress is closely related to stabilization of atherosclerotic plaque and ACS (Nguyen et al. 2019). Additionally, Lavall et al. suggested that the oxidative profile created by STEMI and NSTEMI was similar regardless of the size of the arterial occlusion created by the thrombus (Lavall et al. 2016).

In conclusion, previous studies dealing with cardiovascular diseases provide strong evidence for the link between the LTL ratio and oxidative stress. However, there are a limited number of studies that provide evidence on the relationship between LTL values and oxidative stress in STEMI and NSTEMI, or state whether they are risk factors. In our study, we demonstrated that OSI levels and LTL values were more statistically significant in STEMI than in NSTEMI, although there were similar risk factors among the groups. Further studies are needed to confirm these findings and explore the potential association between LTL, STEMI, and NSTEMI.

5 Study Limitations

Firstly, we conducted a local study where the number of patients was kept relatively low. However, we carefully selected STEMI and NSTEMI patients based on various demographic and clinical features that may adversely affect the interpretation of our results. Secondly, these results based on the telomere length were measured in blood leukocytes, and the telomere length to be measured in other tissues, such as vascular tissue, may show a stronger correlation with STEMI and NSTEMI. Our analyses reflected the measurement of telomere length at a single time point. Long-term changes in telomere length at different time intervals as a result of years of monitoring of patients may show stronger associations with disease risk. The rate of active smoking and family history was higher in the STEMI group compared to the NSTEMI group. This may explain the significant linkage of oxidative stress and LTL with STEMI, but further studies are needed to validate the findings. The final limitation was that we did not take into account the leukocyte subpopulation distributions, a factor that can determine LTL measurement and the relationship of this parameter to cardiac dysfunction (Blackburn et al. 2015).

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Conflict of Interest The authors report no relationships that could be construed as a conflict of interest.

Authors' Contributions All authors read and approved the final version of the manuscript.

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